Reviews

Inorganic Arsenic: A Need and an Opportunity to Improve Risk Assessment

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This paper presents views on the current status of (inorganic) arsenic risk assessment in the United States and recommends research needed to set standards for drinking water. The opinions are those of the Arsenic Task Force of the Society for Environmental Geochemistry and Health, which has met periodically since 1991 to study issues related to arsenic risk assessment and has held workshops and international conferences on arsenic. The topic of this paper is made timely by current scientific interest in exposure to and adverse health effects of arsenic in the United States and passage of the Safe Drinking Water Act Amendments of 1996, which has provisions for a research program on arsenic and a schedule mandating the EPA to revise the maximum contaminant level of arsenic in drinking water by the year 2001. Our central premise and recommendations are straightforward: the risk of adverse health effects associated with arsenic in drinking water is unknown for low arsenic concentrations found in the United States, such as at the current interim maximum contaminant level of 50 µg/l and below. Arsenic-related research should be directed at answering that question. New epidemiological studies are needed to provide data for reliable dose–response assessments of arsenic and for skin cancer, bladder cancer, or other end-points to be used by the EPA for regulation. Further toxicological research, along with the observational data from epidemiology, is needed to determine if the dose–response relationship at low levels is more consistent with the current assumption of low-dose linearity or the existence of a practical threshold. Other recommendations include adding foodborne arsenic to the calculation of total arsenic intake, calculation of total arsenic intake, and encouraging cooperative research within the United States and between the United States and affected countries. *Key words:* arsenic, cancer, dose response, drinking water, food, risk assessment. *Environ Health Perspect* 105:1060–1067 (1997). *http//ehis.niehs.nih.gov*

In selected regions of the world, long-term ingestion of arsenic at relatively high concentrations in drinking water has been associated with disorders of the skin ranging from hyperpigmentation or hypopigmentation and hyperkeratosis to various skin cancers; with cancers of the bladder, liver, lung, kidney, colon, and other internal organs; with peripheral vascular disorder that may include blackfoot disease; and with other confirmed or suspected adverse effects including diabetes, ischemic heart disease, reproductive effects, and impairment of liver function (*1–17*). Observed toxicity has largely been associated with inorganic arsenic, which is the focus of this paper. These adverse health effects have been observed in locations where arsenic leaches into well water or thermal springs from the substratum or percolates into surface water from soil rich in volcanic sediment, as may be found in Bangladesh, West Bengal India, Thailand, Taiwan, China, Inner Mongolia, Mexico, Argentina, Chile, Finland, and Hungary (*18–27*). Remediation has reduced arsenic concentrations in water used for drinking or irrigation in some locations but not in others. In India and Bangladesh, for example, hundreds of thousands of persons are currently exposed to highly toxic levels of arsenic in water from tube wells used for drinking and irrigation (*18–21*).

In the United States, total nonoccupational exposure to inorganic arsenic (hereafter called arsenic) from all routes is primarily by ingestion of water and food (*28–34*). Exposure in the United States from fossil fuel combustion is now relatively low (*35,36*). Air emissions of arsenic from mineral processing and smelting have decreased during the past two decades due to the increased effectiveness of air pollution controls and metal refining processes. Ingestion of arsenic in soil remains a potential but limited route of exposure for young children in most situations. Typical daily intake from food for a U.S. adult is on the order of 10–30 µg/day (*30,34*). The drinking water of about 98% of the U.S. population is below 10 µg/l (*28*), well below the current interim maximum contaminant level (MCL) of 50 µg/l, but some portion of the remaining 2% of the population use drinking water with arsenic concentrations that may reach 50–100 µg/l (*31*). The EPA (*1*) assumes for its risk calculations (where risk is the increased chance that an individual will develop skin cancer from lifetime daily arsenic intake of a specified amount) that a U.S. adult consumes 2 liters water/day. Thus, total intake of arsenic from food and water is a few tens of micrograms per day for most people in the United States, but much higher for some people in areas with high arsenic concentra-

tions in drinking water. If there is a health risk at intake of a few tens of micrograms per day, then nearly everyone in the U.S. population is at some risk from exposure to arsenic. The size of the U.S. population at risk and the magnitude of the risk depend critically on the toxicity of long-term exposure to small doses of arsenic.

The areas of relatively high arsenic concentrations in drinking water in the United States are mostly communities in the western and southwestern states and Alaska, typically served by one or more small water systems. One of the largest U.S. communities with elevated arsenic in drinking water is Hanford, California. Epidemiological studies of health effects in high-arsenic regions of the United States have not shown an impact of arsenic, but sample sizes tended to be small (*37,38*). The World Health Organization has adopted a provisional guideline for drinking water of 10 µg/l (*32*), and Canada has lowered its guideline to 25 µg/l, considered an interim value with intent to lower further (*33*). Both guidelines were based on risk calculations for skin cancer from the Taiwan study used in the 1988 EPA risk assessment (*1*). A reduction of the MCL in the United States to 10 µg/l would not have much impact on human exposure for most of the U.S. population, but it could significantly reduce the exposure in selected small populations. Reductions below 10 µg/l would increasingly affect a larger portion of the U.S. population.

The potential to determine the nature and magnitude of health risks at low daily intakes typical of the United States is limited by the lack of a good animal model for experimentation, inadequate dose–response data on humans, and incomplete knowledge of the uptake, biotransformation, and distribution of arsenic in the body. Drinking water in locations where arsenicism (arsenic-induced skin disorders) and more severe disorders have been observed are relatively high. There is no direct observational evidence that demonstrates severe disorders at less than several hundred micrograms per liter.

At the low end of the exposure scale, arsenic toxicity may not persist down to zero concentrations. For example, the current EPA risk assessment of arsenic (*1*) notes that "experimental studies with rats, chicks, minipigs, and goats demonstrate the plausibility that arsenic, at least in inorganic form, is an essential nutrient," but adds that nutritional essentiality for humans has not been established [also see Uthus (*39,40*)]. Aside from whether trace amounts of arsenic may be beneficial, some mechanistic studies on metabolism, genotoxicity, and other factors suggest the dose–response relationship may be nonlinear, i.e., there may

either be a threshold (dose level below which there is no effect) or the dose is relatively less effective at low levels. As will be discussed, however, consensus is lacking on the nonlinearity issue, and even if the concept is correct, there is a limited basis for incorporating it into dose–response assessment at the individual or population level. Thus, the magnitude of the risk of adverse health effects at the current MCL for drinking water in the United States is unknown. The current information is inadequate as a basis for determining the MCL.

Responsibility for setting the MCL for arsenic in drinking water lies with the EPA under the Safe Drinking Water Act (SDWA). The EPA risk assessment for arsenic is also used as the basis for evaluating the need for remedial actions for soil at hazardous waste sites listed under Superfund (*41*). The current MCL of 50 µg/l was set in the National Interim Primary Drinking Water Regulation of 1976 to protect against chronic toxicity rather than cancer. An EPA risk assessment based on the lifetime risk of skin cancer appeared as a special report of EPA's Risk Assessment Forum in 1988 [(*1*); see also Brown et al. (*42*)], but the MCL was not subsequently revised. In 1996, Congress passed the Safe Drinking Water Act Amendments (*43*) with a provision that requires the EPA to propose a regulation for arsenic in drinking water not later than 1 January 2000 and to issue a final regulation a year later.

Thus, it is timely to consider regulatory methods of cancer risk assessment and research needs in relation to arsenic. The EPA, the American Water Works Association Research Foundation (AWWARF), and the Association of California Water Agencies have recently pooled resources totaling $3 million to fund additional arsenic-related research. Following the schedule mandated by the 1996 Safe Drinking Water Act Amendments (*43*), the EPA has drafted a lengthy research plan for arsenic. This paper describes issues central to risk assessment of arsenic, including an overview of regulatory procedures and default assumptions used for risk assessment, and makes recommendations to improve risk assessment of arsenic. A description of who we are, and the reasoning behind our recommendations, is set forth in the sections that follow.

The SEGH Arsenic Task Force

The SEGH Arsenic Task Force is a group of scientists assembled under the auspices of the Society for Environmental Geochemistry and Health (SEGH), an international professional society specializing in methods for assessing exposure to trace elements in the environment and the health

and environmental impacts from such exposure. A similar SEGH task force on lead has produced a book (*44*) and a review article (*45*). This commentary reflects our views as individual scientists and not the views of the academic, industry, government, or consulting/contract research organizations with which we are associated.

We view arsenic as an example of a substance for which better scientific information is needed to improve risk assessment needed for regulatory decisions. The SEGH held a special session on arsenic at its annual meeting in 1991 (*46*) and subsequently organized international conferences on arsenic in 1993 (*3*) and 1995 (*4*). Between these meetings, SEGH held a specialized Workshop on Arsenic Epidemiology and Pharmacokinetic Modeling in Annapolis, Maryland, in 1994.

How U.S. Regulatory Agencies Estimate Cancer Risk

U.S. regulatory agencies presently conduct cancer risk assessments using the default assumption that carcinogens do not have a threshold (*47*) and that excess risk is proportional to dose at low values (commonly referred to as low-dose linearity). The present EPA risk estimate for arsenic (5×10^{-5} lifetime risk of cancer per microgram per liter of arsenic in drinking water), which is based on this default assumption, implies that a large part of the U.S. population is at risk from present levels of arsenic in food and drinking water. The real risk, however, critically depends on the shape of the dose–response curve at low arsenic concentrations, which cannot be accurately determined from current epidemiologic data. Four hypothetical shapes of a dose–response relationship are plotted in Figure 1 (these curves are for illustration of concepts and have not been fit to actual data on arsenic). The risk of health effects or response is shown on the vertical axis in Figure 1, and the exposure as a daily ingested quantity or dose is shown on the horizontal axis. The default assumptions used by the EPA for
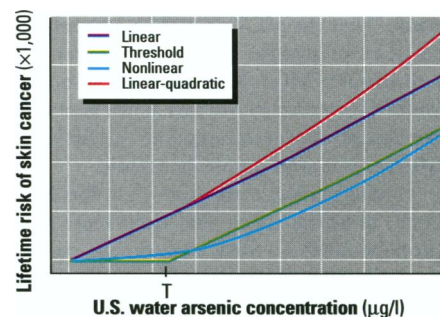

Figure 1. Examples of dose–response relationships. The threshold (T) is placed arbitrarily for illustration.

risk assessment lead to a dose–response function that is linear at low exposures, as illustrated by the linear and linear-quadratic curves. The probability of the health effect, or risk, is about equal for both those curves and proportional at the low end of the exposure range.

For the threshold curve, the risk is zero below a threshold (T; arbitrarily placed on the figure for illustration), but proportional to dose above T. The nonlinear curve shows a relationship in which some risk is still present below T, but the slope, or risk per unit exposure, decreases as the arsenic concentration gets lower. In this case T might be regarded as a practical threshold for regulatory purposes. The sublinear function illustrated by the nonlinear curve rarely can be measured accurately enough to determine the details of its shape or to distinguish it from the threshold curve.

Application to arsenic. The epidemiological data used for the EPA risk estimate for arsenic came from a study in Taiwan carried out in the 1960s (5,6), in which arsenic concentrations in drinking water were as much as 1,400 µg/l. Recent research indicates there may have been additional arsenic exposure through food (48,49), so total arsenic intake approached 3,000 µg/day for some people in the areas studied. A linear plus quadratic relationship, illustrated in Figure 1, was used in the EPA risk assessment (1). At levels of a few tens of micrograms per day relevant to exposure from food and water in the United States, the contribution of the quadratic term is negligible.

The EPA estimates the annual cost of compliance for drinking water treatment at $24 million for the current MCL of 50 µg/l and $2.1 billion for an MCL of 2 µg/l (50). These figures do not include start-up costs and increased costs of remediation. If the correct form of the dose–response relationship is more akin to the general shape of the threshold or nonlinear curves than the linear or linear-quadratic curves (Fig. 1), the MCL for a fixed lifetime risk would be higher and less (possibly much less) costly to implement. That the MCL should be correctly set to protect public health, whatever the appropriate MCL level may be, is not at issue. Our concern on this point lies with the default assumption used by the EPA and whether it is appropriate for arsenic.

Some evidence suggests that the incidence of health effects may drop more than proportionally to dose, making the correct dose–response shape resemble the threshold or nonlinear curves in Figure 1. The evidence includes metabolic studies in animals (51), metabolic studies in human populations consuming drinking water with high levels of arsenic (22), clinical studies of a small number of human volunteers (52), and genotoxicological studies of the arsenic dose–response relationship (53). Some recent analyses of epidemiological data also add to the uncertainty about the EPA's linear-at-low-dose assumption for arsenic (54,55). Conflicting evidence has led to contention, however, supporting the need for further research. For example, Hopenhayn-Rich et al. (56) concluded that human studies do not support a methylation threshold hypothesis. They analyzed data from studies that measured urinary inorganic arsenic and the metabolites monomethylarsonic acid (MMA) and dimethylarsenic acid (DMA) in different populations; they found that, on average, 20–25% of inorganic arsenic remains unmethylated regardless of the exposure level. Further discussion of these issues has appeared elsewhere (57–63). These studies may be contrasted with equally recent studies from Mexico that do show an impact of arsenic dose on methylation, particularly when considered in terms of the DMA:MMA ratio (64,65).

If a practical threshold (as illustrated by the nonlinear curve in Fig. 1) for chronic arsenic toxicity does exist, the public health benefit from large expenditures to reduce arsenic levels in water and soil will be small, perhaps negligible. The magnitude of these expenditures should be a strong incentive to discover whether such a practical threshold is evident in the human data. Because of the need to improve the quality of the measurements of both arsenic exposure levels and health effects in the existing studies, such a determination will require additional research.

Under a directive from Congress, the National Academy of Sciences (NAS) recently reviewed the EPA's risk assessment methodology for environmental carcinogens (47). The NAS supported the EPA's use of default assumptions (including those leading to a dose response that is linear at low exposure, as in the linear and linear-quadratic curves of Fig. 1) in the absence of scientific information to the contrary. But, the NAS urged that the defaults be replaced when scientific information can provide a better basis for assessing risk. Arsenic is an example in which the scientific information to support better risk assessment should be obtainable, probably within 5–10 years and at a cost that is very small compared to the economic and public health stakes involved (66,67). Prior to the NAS report, the EPA Science Advisory Board (SAB) recommended that the EPA replace its risk assessment (1) with an approach that includes information on potentially nonlinear mechanisms for detoxification of arsenic (68). A subse-

quent 1992 SAB report proposed a detailed research program to support improved risk assessment (69), but this program was not funded by the agency. Additional information has appeared since the SAB reports that reinforces the potential to improve arsenic risk assessment (70).

Limitations of Information on Arsenic

Biological mechanisms of arsenic toxicity. Inorganic arsenic is detoxified in the body by enzymatic methylation. Methyl groups are added sequentially to yield MMA and DMA. The acute toxicity of the arsenic species decreases about an order of magnitude with each additional methyl group (as measured by the lethal dose, LD_{50}). MMA and DMA do not appear to cause DNA mutations (i.e., they are not genotoxic) except at high doses (71); thus, they are believed to pose only minimal toxicological risk. The evidence suggests that toxicity results from the remaining inorganic arsenic that is not methylated. For example, a recent skin organotypic model for arsenic demonstrated that arsenic, but not MMA or DMA, caused cellular changes with a cancerous appearance (72).

Several physiologically based pharmacokinetic (PBPK) models are being developed that relate intake of inorganic arsenic to concentrations in tissue and, along with metabolites MMA and DMA, in urine (73–76). Recent observations from humans exposed to relatively high levels of arsenic in drinking water indicate a need to determine ratios of inorganic arsenic, MMA, and DMA as measured in urine, rather than just the inorganic arsenic exposure, to evaluate the saturation of metabolic detoxification processes (22,77). It is important to recognize that saturation of arsenic metabolism does not mean that no detoxification of arsenic occurs above a certain exposure level, but that the relative effectiveness is decreased above that exposure level.

Toxicological studies, primarily in animals, demonstrate that nutritional deficiencies can result in impaired arsenic metabolism (78). Thus, nutritional deficiencies may contribute to the high incidence of arsenic-induced human health effects in India and Taiwan (13–15). The 1989 SAB report (68) noted that subgroups of the population with reduced methylating capability may be more prone to arsenic-induced cancer and other health effects. The recent NAS report on risk assessment (47) emphasizes the potential importance that genetic and nutritional factors may have in causing risk levels to vary among subgroups in the population. Such variability may occur both between and within countries.

Existing epidemiological studies. Although a large number of studies on exposure or health effects related to arsenic are either under way or completed, there are only two major studies, both from Taiwan, that link cancer prevalence or mortality with exposure to arsenic at different drinking water concentrations (which we refer to as dose–response data) (5–9). These studies demonstrate a dose–response relationship for cancer at various sites and arsenic concentrations in water, but the data are not sufficiently precise for accurate quantitative assessment of the magnitude of cancer risk at different arsenic concentrations needed to set an MCL in the United States because the studies report exposures for groups of people rather than for individuals. (Such studies are referred to as ecological studies.)

For example, the Tseng study (5,6) used in the 1988 EPA risk assessment collected skin cancer data on individuals, but relied on a previous study for exposure data on wells tested for arsenic concentrations. Participants were identified with a village but not with the specific well within the village used for drinking water. In some villages, only one well was tested, and in those with multiple tests, the outcomes covered a wide range. The health effects were first grouped by village, with the average well concentration used as the exposure index for the whole village. The health effects data were then combined across villages with an exposure index in the same interval, 0–300 µg/l, 300–600 µg/l, or >600 µg/l. The well tests and average value for each village were not reported in the published study (5). An attempt to reconstruct the exposure data by village in the Tseng study found that villages categorized in the 0–300 µg/l group probably contained some wells with concentrations as high as 770 µg/l (79). Brown et al. (80) provide a more general discussion of uncertainty in arsenic risk assessment that includes bladder cancer.

Other factors contribute further to uncertainty in the exposure of individuals in the Tseng study: arsenic concentrations may have varied temporally within the same well, as noted by Tseng (5); a person may not have used the same water source throughout a lifetime, particularly if a change of residence occurred; and the method used for the determination of arsenic in the wells [attributed to Natelson (5)] has poor accuracy and precision below 50 µg/l (81). In addition to drinking water, food is an important contributor to total intake of arsenic. Although data on the arsenic content of foods in Taiwan are limited, it is clear that a large difference in arsenic intake from food between the affect-ed region of Taiwan and the United States would have a substantial impact on the estimates of lifetime risk from arsenic in drinking water in the United States (48,49).

Research Needs

Epidemiology. New epidemiological studies are needed to provide better information on the shape of the dose–response relationship. As noted previously, there are locations outside the United States where arsenic exposure is current, or sufficiently recent, that might be considered as potential study sites. The central requirement is to match, in a study population of ample size and range of arsenic exposure histories, the presence or absence of adverse health effects in individuals with knowledge of their long-term exposure to arsenic. The range of exposure would ideally include drinking water concentrations below the current MCL of 50 µg/l to a few hundred micrograms per liter and, if possible, to 1,000 µg/l. These requirements might be met by an ongoing study, as in Chile, but current and historical information is very limited.

To conduct a dose–response study, one would need to evaluate the feasibility and alternatives in candidate locations, such as Bangladesh, West Bengal India, Thailand, Taiwan, China, Inner Mongolia, Mexico, Argentina, Chile, Finland, and Hungary. Ideally, a study population would be stationary, with individuals having been exposed to drinking water of known arsenic concentrations for an extended and known duration. Similarly, the contribution of arsenic from food would need to be known, and arsenic from all sources would need to be speciated. In some countries such as Taiwan, Hungary, and Mexico, remediation of arsenic concentrations in drinking water in endemic regions may pose limitations on reconstruction of exposure histories and the health endpoints that could be evaluated in relation to that history. For example, in some regions of Mexico, drinking water concentrations of arsenic were high until about 5 years ago, when exposures were reduced. Such a location may still be suitable to study an endpoint such as cancer, which has a long latency period, but not to study biomarkers of current exposure.

Some health endpoints may not have as extended a latency period as cancer, or the effects of exposure duration may be unknown, e.g., cardiovascular disease or adverse pregnancy outcome. Thus, the health endpoints that may be studied in a location, the existence of medical records and arsenic exposure histories, and the type of epidemiological study (case–control, retrospective cohort, prevalence, etc.) that might be conducted are interrelated, making it necessary to assess the potential for each candidate study location separately. There are, of course, additional issues related to cooperation and participation by the host country: existence of personnel, facilities, and other resources and the cost and duration to complete a study. The AWWARF is currently funding a project to study the feasibility of conducting epidemiological studies on arsenic, following research recommendations from a workshop held in 1995 (70).

Although previous epidemiological studies in the United States have not found evidence of excess cancer associated with arsenic exposure, further investigations are under way that include endpoints such as cardiovascular disease. However, the small number of people exposed to relatively high arsenic levels in the United States and the limited range of exposure make the United States an unlikely location for a dose–response study. Additionally, the U.S. population is relatively mobile, making it difficult to estimate arsenic exposure over several decades of a lifetime. By contrast, some populations with high arsenic exposure outside the United States are relatively stationary, thus providing a better opportunity to assess lifetime exposure. Also, exposed populations are much larger than in the United States and exhibit a much wider range of exposure over which to observe the shape of the dose–response relationship. Epidemiological study designs to address potential high bladder cancer risks from arsenic in drinking water are discussed by Vahter and Marafante (78).

Combining epidemiological with mechanistic studies in highly exposed populations. Biomarkers are indicators in biological media (e.g., urine, blood) that can be used to measure either exposure or an effect of exposure. A useful biomarker of recent exposure to arsenic is inorganic arsenic and its methylated metabolites in urine. Quantification of inorganic arsenic and its metabolites in urine can provide important information on detoxification mechanisms that influence the actual dose to tissues and hence potential risk for cancers and other chronic health effects. It may be possible to use data from urine or other fluids or tissue samples in epidemiological studies to correlate biological changes with the potential for health effects.

Biomarkers of effect have only recently been applied to arsenic research. An example of a biomarker of effect of arsenic is the presence of micronuclei in exfoliated bladder cells in urine (82), although this effect is not specific to arsenic. Such biomarkers can help us understand the disease processes and improve risk assessment.

Biomarkers may be very important in providing information on the mechanistic relationship between arsenic exposure and internal dose or between arsenic exposure and cancer, or other adverse health effects. For example, biomarkers may help to verify and estimate parameters for PBPK models and to confirm whether certain types of lesions or cell alterations are precursors to cancer. Because there are no known biomarkers of effect specific to arsenic, population studies using such biomarkers must consider the sensitivity of such markers, as well as address confounding exposures.

Exposure data for individuals over a time scale of decades, combined with mechanistic information and individual health histories, would be the best basis for determining the correct dose–response relationship. Data indicating the presence or absence of a practical threshold would have very important implications for improving the risk assessment for arsenic. Evidence indicating that such a practical threshold exists would indicate that the EPA's default assumption of low-dose linearity is incorrect for arsenic. Even stronger evidence would be provided by confirmation of a mode of action for which a practical threshold is biologically plausible and a linear relationship is much less plausible. Such a mode of action might involve saturation of a detoxification mechanism, interference by arsenic species with cellular DNA repair processes such those governed by the *p53* oncogene (*53,83*), or other possible mechanisms; these mechanisms may be elucidated by further research on highly exposed human populations, supplemented by mechanistic research in whole animals and *in vitro* cellular studies.

Improved Risk Assessment Is Needed to Manage the Risks

There is some inconsistency in federal regulation of arsenic by different organisms. For example, there is no regulation of arsenic in food, although food is the major source of arsenic for most Americans. The Food and Drug Administration (FDA) regards arsenic as a natural constituent in food and is thus acceptable by default. On the other hand, the EPA is legally required to set allowable standards for arsenic in drinking water and in water and soil at Superfund sites.

Superfund guidance requires consideration of soil screening levels (SSLs), which are chemical concentrations in soil below which there is no concern for human health risk (*41*). An exceedance of the SSL does not indicate the automatic need for remedial action at a Superfund site, but rather the need for further analysis. For carcinogens, the EPA sets SSLs at the soil concentration associated with a 10^{-6} risk. In the case of arsenic, the SSL is 0.4 mg/kg, which is below the geometric mean arsenic concentration of 5 mg/kg for soils in many areas of the United States (*84*). Thus, arsenic in soil at background levels represents a natural source of arsenic exposure.

The requirement of the EPA to revise the MCL for arsenic in drinking water has maintained interest in the 1988 EPA skin cancer risk assessment; there has been discussion of possible reductions in the MCL to 20 µg/l, 5 µg/l, or even 2 µg/l. As noted previously, such reductions would incur large costs to remove arsenic during water treatment (*50*), costs that would be passed on to the public. Expenditures for soil remediation would also increase as arsenic levels of 10–100 mg/kg and higher are found near former copper mines and smelters, manufacturing sites, and agricultural areas where arsenical pesticides were used in the nineteenth and early twentieth centuries and at other locations where arsenic compounds were used and then discarded (*85*). The issue here is not the dollar value of public health, but the large uncertainty in how much the MCL may need to be reduced to protect public health.

Recommendations of the SEGH Arsenic Task Force for Arsenic Research in Support of Risk Assessment

• Research is needed to improve risk assessment of arsenic without regard to the regulatory timetable. Current disagreements on issues related to arsenic toxicity and exposure are largely due to incomplete information needed for risk assessment and perhaps to limitations of current risk assessment methodology. Scientific information relevant to health effects assessment of arsenic has advanced significantly during the past decade, and research needs to be continued on its own time schedule. Arsenic provides a good case study for improving cancer risk assessment methods to include information about modes of action and to investigate possible departure from the no-threshold default assumption of low-dose linearity in accordance with the 1994 recommendations from the National Academy of Sciences (*63*). The NAS recommendations have been accepted in principle by the EPA (*86*), and they have motivated many of the changes in the EPA's proposed revision of its cancer risk assessment guidelines (*87*). Thus, we see further research on arsenic as necessary to

improve risk assessment of arsenic in drinking water and as an opportunity to advance cancer risk assessment methods.
• More collaborative research should be undertaken within the United States between government agencies and other interested parties and between the United States and other countries with similar research interests in arsenic. Because so many countries have serious arsenic-related health problems, there are excellent opportunities for international collaboration and cooperation. The EPA draft arsenic research plan alludes to collaboration with Chile and India for dose–response assessment of cancer at internal sites, but to our knowledge, no agreements are in place. Affected portions of U.S. industry have indicated a willingness to co-fund research, including research outside of the United States. A large step in this direction is the cooperation of the EPA, AWWARF, and the Association of California Water Agencies in soliciting applications to support up to $3 million of arsenic-related research. We encourage funding groups to consult the recommended list of research projects from the 1992 SAB report (*69*), the recent EPA workshop on arsenic epidemiology (*88*), the report of the AWWARF workshop on research needs (*71*), and the draft EPA arsenic research plan. Projects currently sponsored by AWWARF may also contribute further to the identification of specific research needs.
• We urge expanded research and completion of a new risk assessment by the year 2000 as an alternative to basing the drinking water MCL on the EPA's 1988 risk assessment. Unlike the two preceding recommendations, this one addresses the short-term need to improve arsenic risk assessment to set the MCL by the year 2000. The EPA draft arsenic research plan is intended to meet this objective, but it takes a very broad perspective with limited setting of priorities. We believe that the current EPA risk assessment on skin cancer is inadequate. This is not the fault of the EPA or of the classic Tseng study (*5,6*) on which the current risk assessment is based; rather, it follows from information learned subsequent to the 1988 EPA risk assessment about characteristics of the exposure data (*80*). While these data provide strong evidence that arsenic in drinking water causes skin cancer and other adverse health effects, they are not well suited for dose–response estimation needed to estimate risk of cancer at low arsenic concentrations in water as found in the United States. Moreover,

the EPA's risk assessment is for skin cancer, although more recent data have become available from Taiwan; these data show a relationship between arsenic and cancer at internal sites, particularly the bladder, which may pose a greater risk than skin cancer (*37*). Our recommendation is to consider what useful research can be completed by the year 2000 that might improve the information base needed to set an MCL. Initially this should include review of relevant research that has appeared since the 1988 risk assessment, in both toxicology and epidemiology, and becoming familiar with ongoing and completed studies in other countries with high-arsenic areas. In our judgment, highest priority should be given to epidemiological and mechanistic research to clarify the shape of the dose–response curve at exposures of 50–500 µg/day, or even lower, if feasible, for skin cancer and alternative endpoints, such as bladder cancer, that might be used to set the MCL.

- The U.S. government should be more consistent in assessing the risk from low levels of arsenic in water, soil, and food. Total arsenic intake from all sources, predominantly food and water in the United States, should be taken into account in setting standards to protect public health, instead of one medium (water) being addressed and another (food) being dismissed. The FDA currently disregards arsenic in food as a health risk because it occurs naturally in the soil. But arsenic is no less toxic in food than water because it is derived from natural sources; arsenic in water is similarly derived from natural sources much of the time. If we judge that 100, 40, or 10 µg/day from water is an unacceptable risk to public health, we should also investigate the extent to which this level is exceeded due to exposure from food. This will require the federal government to coordinate its activities and objectives to protect public health from harmful environmental substances.

REFERENCES

1. U.S. EPA. Risk Assessment Forum, Special Report on Ingested Inorganic Arsenic: Skin Cancer, Nutritional Essentiality. EPA 625/3-87-013. Washington, DC:U.S. Environmental Protection Agency, 1988.
2. Hutchinson J. On some examples of arsenic-keratosis of the skin and arsenic-cancer. Trans Pathol Soc Lond 39:352–363 (1888).
3. Chappell WR, Abernathy CO, Cothern CR, eds. Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16. Middlesex, England:Northwood, 1994.
4. Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic Exposure and Health Effects. New York:Chapman & Hall, 1997.
5. Tseng W-P, Chu HM, How SW, Fong JM, Lin CS, Yen S. Prevalence of skin cancer in an endemic area of chronic arsenism in Taiwan. J Natl Cancer Inst 40:453–463 (1968).
6. Tseng W-P. Effects and dose–response relationship of skin cancer and blackfoot disease with arsenic. Environ Health Perspect 19:109–119 (1977).
7. Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. Br J Cancer 53:399–405 (1986).
8. Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res 45:5895–5899 (1985).
9. Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. Br J Cancer 66:888–892 (1992).
10. Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, Smith AH. Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiology 7:117–124 (1996).
11. Sancha AM, Rodriguez D, Vega F, Fuentes S, Salazar AM, Venturino AM, Moreno V, Baron AM. Human exposure to arsenic in water: a study of Atacamenan settlements in northern Chile. In: Book of Abstracts from SEGH International Conference on Arsenic Exposure and Health Effects, 28–30 July 1993, New Orleans, LA. Denver, CO:University of Colorado, 1993;68.
12. Chen C-J, Lin LJ, Hsueh YM. Ischemic heart disease induced by inorganic arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994; 83–90.
13. Guha Mazumder DN, Das Gupta J, Santra A, Pal A, Ghose A, Sarkar S, Chattopadhaya N, Chakraborti D. Non-cancer effects of chronic arsenicosis with special reference to liver damage. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997; 112–123.
14. Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. Artherogenicity and carcinogenicity of high-arsenic artesian well water. Arteriosclerosis 8:452–460 (1988).
15. Hsueh YM, Cheng GS, Wu MM, Yu HS, Kuo TL, Chen CJ. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. Br J Cancer 71:109–114 (1995).
16. Smith AH, Hopenhayn-Rich C, Bates MN, Goeden HM, Hertz-Picciotto I, Duggan HM, Wood R, Kosnett MJ, Smith MT. Review of cancer risks from arsenic in drinking water. Environ Health Perspect 97:259–267 (1992).
17. Bates MN, Smith AH. Arsenic ingestion and internal cancers: a review. Am J Epidemiol 3:462–476 (1992).
18. Chatterjee A, Das D, Mandal BK, Samanta G, Banerjee P. The biggest arsenic calamity in the world. Analyst 120:643–650 (1995).
19. Chowdhury TR, Mandal BK, Samanta G, Basv GK, Chowdhury PP, Chanda CR, Karan NK, Lodh D, Dhar RK, Das D. Arsenic in groundwater in six districts of West Bengal, India—The biggest arsenic calamity in the world: the status report up to August, 1995. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;93–111.
20. Saha KC. Chronic arsenical dermatosis from tube-well water in West Bengal during 1983–87. Indian J Dermatol 40:1–12 (1995).
21. Pearce F. Death and the devils water. New Scientist 147:14–15 (1995).
22. Del Razo LM, Hernandez JL, Garcia-Vargas GG. Urinary excretion of arsenic species in a human population chronically exposed to arsenic via drinking water. A pilot study. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994; 91–100.
23. Cebrian ME, Abores A, Aguilar M, Blakely E. Chronic arsenic poisoning in the north of Mexico. Hum Toxicol 2:121–133 (1983).
24. Niu S, Cao S, Shen E. The status of arsenic poisoning in China. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;73–83.
25. Foy H, Tarmapai S, Eamchan P, Metdilogkul O. Chronic arsenic poisoning from well water in a mining area in Thailand. Asia-Pac J Public Health 6:150–152 (1992/1993).
26. Choprapawon C, Rodcline A. Chronic arsenic poisoning in Ronpibool Nakhon Si Thammarat, the southern province of Thailand. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;69–77.
27. Luo ZD, Zhang YM, Ma L, Zhang GY, He X, Wilson R, Byra DM, Griffiths JG, Lai S, He L. Chronic arsenism and cancer in Inner Mongolia—consequences of well-water arsenic levels greater than 50 µg/l. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;55–68.
28. Reid J. Arsenic occurrence: USEPA seeks clearer picture. Special Issue: Arsenic: the Quest for Answers. Am Water Works Assoc J 86:44–51 (1994).
29. Pontius FW, Brown KG, Chen CJ. Health implications of arsenic in drinking water. Special Issue: Arsenic: the Quest for Answers. Am Water Works Assoc J 86:52–63 (1994).
30. Borum DR, Abernathy CO. Human exposure to inorganic arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;21–30.
31. Davis MK, Reich KD, Tikkanen MW. Nationwide and California occurrence studies. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994; 31–40.
32. World Health Organization. Guidelines for

drinking-water quality: Recommendations, Vol I. Geneva:World Health Organization, 1993.

33. Hughes K, Meek ME. Arsenic in the Canadian general environment—evaluation of risks to health. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994; 257–268.

34. Adams MA, Bolger PM, Gunderson EL. Dietary intake and hazards of arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994; 41–50.

35. Lamarre L. The risks of utility hazardous air pollutants. Electric Power Research Institute J 20:6–15 (1995).

36. Electric Power Research Institute. Electric Utility Trace Substances Synthesis Report. EPRI-TR-104614. Palo Alto, CA:Electric Power Research Institute, 1994.

37. Office of Health and Environmental Assessment. Health Assessment Document for Inorganic Arsenic. EPA-600/8-83-021F. Washington, DC:U.S. Environmental Protection Agency, 1984.

38. Valberg PA, Beck BD, Boardman PD, Cohen JT. Likelihood ratio analysis of skin cancer prevalence associated with arsenic in drinking water in the U.S. Environ Geochem Health (in press).

39. Uthus EO. Evidence for arsenic essentiality. Eviron Geochem Health 14:55–58 (1992).

40. Uthus EO. Arsenic essentiality studies and factors affecting its importance. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;199–208.

41. U.S. EPA. Soil Screening Guidance Technical Background Document. Office of Solid Waste and Emergency Response. EPA/540/R-95/128, PB96-963502. Washington, DC:U.S. Environmental Protection Agency, 1996.

42. Brown KG, Boyle KE, Chen CW, Gibb HJ. A dose–response analysis of skin cancer from inorganic arsenic in drinking water. Risk Anal 9:519–528 (1989).

43. Safe Drinking Water Act Amendments of 1996. U.S. Public Law 104-182, 1996.

44. Society for Environmental Geochemistry and Health. Lead in Soil: Task Force Recommended Guidelines (Wixson BG, Davies BE, eds). Northwood, England:Science Reviews, 1993.

45. Wixson BG, Davies BE. Guidelines for lead in soil: proposal of the Society for Environmental Geochemistry and Health. Environ Sci Technol 28:26A–31A (1994).

46. Fowle JR, ed. Environ Geochem & Health 14, 1992.

47. National Research Council. Science and Judgment in Risk Assessment. Washington, DC:National Academy Press, 1994.

48. Brown KG, Abernathy CO. The Taiwan skin cancer risk analysis of inorganic arsenic ingestion: effects of water consumption rates and food arsenic levels. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;260–271.

49. Schoof RA, Yost LJ, Valberg PA, Beck BD. Recalculation of the oral arsenic reference dose and cancer slope factor using revised assumptions of inorganic arsenic intake from food. Toxicologist 14:51 (1994).

50. Kempic JB. Arsenic removal technologies: an evaluation of cost and performance. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;393–405.

51. Vahter M. Species differences in the metabolism of arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;171–180.

52. Buchet JP, Lauwerys R. Inorganic arsenic metabolism in humans. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;181–190.

53. Rudel R, Slayton TM, Beck BD. Implications of arsenic genotoxity for dose-response of carcinogenic effects. Regul Toxicol Pharmacol 23:87–105 (1996).

54. Brown KG, Chen CJ. Significance of exposure assessment to analysis of cancer risk from inorganic arsenic in drinking water in Taiwan. Risk Anal 15:475–484 (1995).

55. Guo HR. Arsenic in drinking water and skin cancer: comparison among studies based on cancer registry, death certificates, and physical examinations. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;243–259.

56. Hopenhayn-Rich C, Smith AH, Goeden HM. Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. Environ Res 60:161–177 (1993).

57. Mushak P, Crocetti AF. Risk and revisionism in arsenic cancer risk assessment. Environ Health Perspect 103:684–689 (1995).

58. Slayton TM, Beck BD, Reynolds KA, Chapnick SD, Valberg PA, Yost LJ, Schoof RA, Gauthier TD, Jones L. Issues in arsenic cancer risk assessment [letter]. Environ Health Perspect 104:1012–1014 (1996).

59. Mushak P, Crocetti AF. Response: accuracy, arsenic, and cancer. Environ Health Perspect 104:1014–1018 (1996).

60. Carlson-Lynch H, Beck BD, Boardman PD. Arsenic risk assessment. Environ Health Perspect 102:354–356 (1994).

61. Smith AH, Biggs ML, Hopenhayn-Rich C, Kalman D. Arsenic risk assessment [letter]. Environ Health Perspect 103:13–15 (1995).

62. Beck BD, Boardman PD, Hook GC, Rudel RA, Slayton TM, Carlson-Lynch H. Response to Smith et al. Environ Health Perspect 103:15–17 (1995).

63. Hopenhayn-Rich C, Biggs ML, Smith AH, Kalman DA, Moore LE. Methylation study of a population environmentally exposed to arsenic in drinking water. Environ Health Perspect 104:620–628 (1996).

64. del Razo LM, Hernandez JL, Garcia-Vargas GG, Ostrosky-Wegman P, de Nava C, Cebrian ME. Urinary excretion of arsenic species in a human population chronically exposed to arsenic via drinking water. In: Arsenic Exposure

and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;91–100.

65. del Razo LM, Garcia-Vargas GG, Vargas H, Albores A, Gonsebatt ME, Montero R, Ostrosky-Wegman P, Kelsh M, Cebrian ME. Altered profile of urinary arsenic metabolites in adults with chronic arsenicism: a pilot study. Arch Toxicol 71:211–217 (1997).

66. North DW, Selker F, Guardino T. The value of research on health effects of ingested inorganic arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;1–20.

67. Fowle III JR. Health effects of arsenic in drinking water: research needs. Environ Geochem Health 14:63–68 (1992).

68. Science Advisory Board. Letter Report to the Administrator. EPA-SAB-89-038. Washington, DC:U.S. Environmental Protection Agency, 1989.

69. Science Advisory Board. Review of Arsenic Research Recommendations. EPA-SAB-DWC-92-018. Washington, DC:U.S. Environmental Protection Agency, 1992.

70. Arsenic in Drinking Water Research Needs Report. Report from the international expert workshop sponsored by the American Water Works Research Foundation, 31 May–2 June 1995, Ellicott City, MD. Denver, CO:American Water Works Research Foundation, 1995.

71. Moore MM, Harrington-Brock K, Cabrera M. Biological effects of arsenic exposure: integration of in vitro genotoxicity data with human biomarker data. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;330–337.

72. Klimecki WT, Borchers AH, Egbort RA, Carter DE, Nagle RB, Bowden GT. Effects of acute and chronic exposure of human-derived keratinocytes on an in vitro human skin equivalent system, a novel model of human arsenicism. Toxicol In Vitro 11:89–98 (1997).

73. McKinney JD. Metabolism and disposition of inorganic arsenic in laboratory animals and humans. Environ Geochem Health 14:43–48 (1992).

74. Menzel DB, Ross M, Oddo SV, Bergstrom P, Greene H, Roth RN. A physiologically based pharmacokinetic model for ingested arsenic. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;209–218.

75. Mann S, Droz PO, Vahter M. A physiologically based pharmacokinetic model for the four arsenic species in mammals. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;219–232.

76. Hsu KH, Froines J, Chen CJ. Studies of arsenic ingestion from drinking water in Northwestern Taiwan: Chemical speciation and urinary metabolites. In: Arsenic Exposure and Health

Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;190–209.
77. Smith AH, Hopenhayn-Rich C, Biggs ML, Moore L, Dale J, Warner M, Bates M, Engel R. Epidemiological study designs to address potential high bladder cancer risks from arsenic in drinking water. In: Arsenic Exposure and Health. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters, Vol 16 (Chappell WR, Abernathy CO, Cothern CR, eds). Middlesex, England:Northwood, 1994;109–118.
78. Vahter M, Marafante E. Effects of low dietary intake of methionine, choline, or proteins on the biotransformation of arsenite in the rabbit. Toxicol Lett 37:41–46 (1987).
79. Brown KG, Guo HR, Kuo TL, Greene HL. Skin cancer and inorganic arsenic: uncertainty-status of risk. Risk Anal 17:37–42 (1997).
80. Brown KG, Guo HR, Greene HL. Uncertainty

in cancer risk at low doses of inorganic arsenic. Hum Ecol Risk Assess 3:351–362 (1997).
81. Gueschonig H, Irgolic KJ. The mercuric-bromide-stain method and the Natelson method for the determination of arsenic: implications for assessment of risks from exposure to arsenic in Taiwan. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997;17–32.
82. Warner ML, Moore LE, Smith MT. Increased micronuclei in exfoliated bladder cells of persons who chronically ingest arsenic-contaminated water in Nevada. Cancer Epidemiol Biomarkers Prev 3:583–590 (1994).
83. Mass MJ, Wang L. Alterations of methylation of the tumor suppressor gene P53: insights into potential mechanisms of arsenic carcinogenesis. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). New York:Chapman & Hall, 1997; 338–348.

84. Connor JJ, Shacklette HT. Background geochemistry of some rocks, soils, plants, and vegetables in the conterminous United States. USGS Professional Paper 574-F. Washington, DC:U.S. Government Printing Office, 1975.
85. Life Systems, Inc. Toxicological Profile for Arsenic (ATSDR). PB93-182376. Washington, DC:U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, 1993.
86. Sussman RM, Goldman LR. Memorandum to EPA Administrator. US Environmental Protection Agency, May 31, 1994. Washington, DC:U.S. EPA Science Policy Council, 1994.
87. U.S. Environmental Protection Agency. Proposed Guidelines for Carcinogen Risk Assessment. Fed Reg 61:17959–18011 (1996).
88. SRA Technologies. An epidemiology research strategy for arsenic in drinking water (Draft), 9 August 1994, Research Triangle Park, NC:U.S. EPA Health Effects Research Laboratory.